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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

Applicant(s): Saran A. Narang et al  
Serial No: 10/031,874 Filing Date: November 14, 2002  
Examiner: David J. Blanchard Art Unit: 1642  
Title: Single-Domain Antigen-Binding Antibody Fragments  
Derived from Llama Antibodies  
Docket No: 11054-1

September 2, 2004

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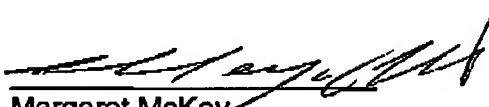
Sir:

SEP 02 2004

This is in Response to the Official Action of June 2, 2004.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment.

Respectfully submitted,

  
Margaret McKay  
Patent Agent for Applicant  
Regn No: 52,519

:sta  
Tel: 613-991-6853

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Margaret McKay

  
September 2, 2004

**IN THE DESCRIPTION**

Kindly substitute enclosed amended description page 12 for description page 12, currently on file.

As is well known to those skilled in the art, the probability of isolating a protein with high affinity or specificity against a target (antibody) of interest increases with the size of the library. Generally, two different types of vectors are used for generating phage display libraries: phagemid vectors and phage vectors.

5 Libraries having size in the order of  $10^8$  can be constructed with relative ease using phagemid vectors. However, a phagemid-based libraries suffers from some serious drawbacks. First, phagemid vectors provide typically a monovalent display and therefore may not select for lower binding (of lower affinity), but potentially important antibody fragments. Second, a phagemid-

10 based library allows for the enrichment of phage particles displaying deleted versions of the antibody fragments. Such particles, often with no binding activity, are preferably selected during the panning process over those displaying the full-length fragments and therefore obscure the process of selection of the full-length binders. Third, constructing a phagemid-based

15 library requires a helper phage and therefore library construction, panning and downstream phage binding assays become a far more complicated and tedious task. For these reasons the use a phage vector for the library construction is preferred.

One of the most widely used phage vectors is fd-tet (Zacher III et al., *Gene*, 9,

20 127-140 (1980)) which consists of fd-phage genome, plus a segment of Tn10 inserted near the phage genome origin of replication. Tn10 contains a tetracycline resistance gene, tetA, and thus confers tetracycline resistance to the host cells carrying the fd-tet vector. It has often been observed that the size of the fd-tet based library was generally low (in the range of  $10^5 - 10^6$ )

25 (Harrison et al., *Methods in Enzymology* [Ed. Abelson, J.N.], 267, 83-109 (1996); Krebber et al., *FEBS Letters*, 377, 277-334 227-231 (1995)), possibly due to the toxic effect of tetA gene product on the host cells. According to the modified procedure of the present invention, the library was propagated as plaques in the absence of tetracycline, resulting in a llama V<sub>H</sub>H library of size

30 of approximately  $8.8 \times 10^8$ . This is the largest size library ever obtained using fd-tet vector. Due to its size, the library has an enhanced probability of selecting therefrom proteins (antibody fragments) binding to almost any given target (antigen).

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